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09/380,534	09/01/1999	THOMAS M. KUNDIG	C9015-2007	2743

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/380,534	KUNDIG, THOMAS M.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/6/03; 10/9/03*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 September 1999* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4/29/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Upon reconsideration, the First Office Action mailed 3/13/03 is hereby vacated and a new First Office Action is follow.

2. Claims 72-91 are pending and are being acted upon in this Office Action.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 72-91 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of obtaining a sustained CTL response in a mammal, which method comprises delivering tumor specific antigen such as the ones disclosed on page 21, virus specific antigen LCMV p33, directly to a lymph node or a lymph vessel of the mammal at a level sufficient to induce CT response in the mammal and maintaining the antigen in the mammal's lymphatic system over time to sustain the CTL response, **does not** reasonably provide enablement for *any* method of obtaining a sustained CTL response as set forth in claims 72-91 for treating *any* disease such as cancer, chronic infectious disease such as hepatitis, and AIDS. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of obtaining a sustained viral specific LCMV p-33 antigen CTL response by implanting a microosmotic pump releasing

mixture of p33 antigen and GM-CSF into the lymphatic system of a mouse over a period of 7 days and the antigen specific CTL response is detected by chromium release assays, and LCMV challenge assays (See page 62 of specification). The specification further discloses that the method of obtaining a sustained tumor antigen specific CTL response in a mammal by direct injection (needle or catheter) into the lymphatic system or implanting a reservoir (pump system, page 55) near a lymphatic organ of an animal to sustain the desired response over time. This regular delivery is achieved by the constant delivery of the antigen at low levels directly to the lymphatic system using an external device or an implantable device. Alternatively, the antigen can be delivered at higher levels to the animal by subcutaneous injection with indirect absorption or equilibration with the lymph system. Delivery on a regular basis is meant to include intermittent (stopping and transmitting at intervals) as well as continuous (transmitting without interruption) delivery (page 9, last paragraph). The specification discloses that the infectious diseases that can be treated using this invention include those caused by pathogens such as bacteria, viruses, protozoa, helminthes, and the like. These diseases include such chronic diseases such as acute respiratory infections, diarrhea diseases, tuberculosis, malaria, hepatitis (hepatitis A, B C, D, E, F virus), measles, mononucleosis (Epsteinebarr virus), whooping cough (pertussis), MDS (human immunodeficiency virus 1 & 2), rabies, yellow fever, and the like (page 17, second paragraph).

The specification does not teach how to make any antigen such as *any* "antigen" in the form of polypeptide, *any* "component" of a microorganism, *any* antigen in the form of a "nucleic acid" encoding the undisclosed antigen, any undisclosed antigen comprises any plasmid, vector, or recombinant viral vector for the claimed method of obtaining a sustained CTL response such as any CTL response because there is insufficient guidance as to the structure such as the amino acid sequence and molecular weight that identified the antigen for the claimed method. Further, the specification does not define the term "component" and fails to teach how to make which "component" of which undisclosed microorganism is effective for the claimed method.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or

deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Since the amino acid sequence of a polypeptide determines its structural and functional properties, without the amino acid sequence of the antigen, the corresponding polynucleotide encoding the undisclosed antigen for the claimed method is not enabled. Likewise, the plasmid such as vector or recombinant viral vector encoding the undisclosed antigen for the claimed method is not enabled.

There is no recognition in the art that sequence with identity predicts biological function. Attwood *et al* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable. Skolnick *et al.*, teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular).

Koga *et al* teach that lymph node injection of antigen such as adjuvant accellerates arthritis than conventional footpad injection in the rat. Furthermore, Koga *et al* teach that lymph node route is more efficient than the conventional route in terms of minimal dose (one fifth of the conventional route) and more consistent appearance of prolonged skin reaction (See abstract, in particular).

Given the indefinite number of antigen, there is insufficient in vivo working example in the specification as filed for the claimed that is effective for treating any disease such as tumor, Hepatitis, and AIDS.

With regard to claim 78, there is insufficient guidance for "disease matched antigen" given the indefinite number of undisclosed disease.

With regard to claim 80, there is insufficient guidance as to which specific cytokine assay is for CTL sustained CTL response. Further, there is insufficient guidance as how increasing life expectancy or observing the health of a mammal correlated with sustained CTL response. With regard to immunofluorescence assay, there is insufficient guidance as what is being detected using said immunofluorescence assay that is correlated with sustained CTL response.

With regard to claim 85, the specification does not define "patient-matched antigen". The specification discloses only HLA matched antigen.

With regard to claim 81, the "adjuvant" in the claimed method directly contradicts the disclosure. The specification on page 14, lines 21-28 discloses that the fundamental improvement of the present method over prior art is that it facilitates the use of inherently non-immunogenic peptide antigens for CTL stimulation **without the combined use of conventional adjuvants**. The specification further discloses that since conventional adjuvants are not required, only the minimal antigenic epitope for a CTL response is required in the formulation (page 14, lines 26-28).

Even if the antigen is limited to viral antigen, there is insufficient in vivo working example demonstrating that the claimed method can treat any disease such as AIDS, common cold, influenza, and cancer. Although the specification discloses the use of one viral specific antigen from LCMV virus in transgenic mice, it is not clear that the reliance of this particular mouse model is effective for HIV, much less sustained CTL response in humans.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

5. Claims 72-91 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *any* method of obtaining a sustained CTL response as set forth in claims 72-91 for treating *any* disease such as cancer, chronic infectious disease such as hepatitis, and AIDS.

The specification discloses only a method of obtaining a sustained viral specific LCMV p-33 antigen CTL response by implanting a microosmotic pump releasing mixture of p33 antigen and GM-CSF into the lymphatic system of a mouse over a period

of 7 days and the antigen specific CTL response is detected by chromium release assays, and LCMV challenge assays (See page 62 of specification). The specification further discloses that the method of obtaining a sustained tumor antigen specific CTL response in a mammal by direct injection (needle or catheter) into the lymphatic system or implanting a reservoir (pump system, page 55) near a lymphatic organ of an animal to sustain the desired response over time. This regular delivery is achieved by the constant delivery of the antigen at low levels directly to the lymphatic system using an external device or an implantable device. Alternatively, the antigen can be delivered at higher levels to the animal by subcutaneous injection with indirect absorption or equilibration with the lymph system. Delivery on a regular basis is meant to include intermittent (stopping and transmitting at intervals) as well as continuous (transmitting without interruption) delivery (page 9, last paragraph). The specification discloses that the infectious diseases that can be treated using this invention include those caused by pathogens such as bacteria, viruses, protozoa, helminthes, and the like. These diseases include such chronic diseases such as acute respiratory infections, diarrhea diseases, tuberculosis, malaria, hepatitis (hepatitis A, B C, D, E, F virus), measles, mononucleosis (Epsteinebarr virus), whooping cough (pertussis), MDS (human immunodeficiency virus 1 & 2), rabies, yellow fever, and the like (page 17, second paragraph).

With the exception of the specific viral antigen from LCMV p-33, there is insufficient written description about the structure associated with function of *any* antigen such as *any* "antigen" in the form of polypeptide, *any* "component" of a microorganism, *any* antigen in the form of a "nucleic acid" encoding the undisclosed antigen, any undisclosed antigen comprises any plasmid, vector, or recombinant viral vector for the claimed method of obtaining a sustained CTL response such as any CTL response without the specific amino acid sequence and the corresponding polynucleotide encoded said undisclosed antigen, much less about which "component" of which undisclosed microorganisms. Since the amino acid sequence of a polypeptide determines its structural and functional properties, without the amino acid sequence of the antigen, the corresponding polynucleotide encoding the undisclosed antigen for the claimed method is not adequately described. It follows that the plasmid such as vector or recombinant viral vector encoding the undisclosed antigen for the claimed method is not adequately described. Given the indefinite number of antigen, there is inadequate written description

about the "antigen" including the patient matched antigen" and the "disease matched antigen".

With regard to claim 80, there is inadequate written description for which specific cytokine to be assay using the "cytokine assay", which molecule to be detected using the "immunofluoresence assays" or "CTL assays" for sustained CTL response in a mammal.

With regard to claim 85, the specification does not define "patient-matched antigen". The specification discloses only HLA matched antigen.

With regard to claim 81, the "adjuvant" in the claimed method directly contradicts the disclosure. The specification on page 14, lines 21-28 discloses that the fundamental improvement of the present method over prior art is that it facilitates the use of inherently non-immunogenic peptide antigens for CTL stimulation **without the combined use of conventional adjuvants**. The specification further discloses that since conventional adjuvants are not required.

Given the infinite number of antigen, the identity of *any* antigen such as *any* "antigen" in the form of polypeptide, *any* "component" of a microorganism, *any* antigen in the form of a "nucleic acid" encoding the undisclosed antigen, any undisclosed antigen comprises any plasmid, vector, or recombinant viral vector for the claimed method is not adequately described. Further, the specification discloses only the specific method using the specific peptide antigen and the specific plasmid for inducing the LCMV specific CTL response, the method of inducing CTL response toward any undisclosed antigen, protein, peptide, nucleic acid is not adequately described. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Given the lack of a written description of *any* additional representative species of antigen as encompassed by the claim method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. Claims 80 and 84 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "cytokine assay, an immunoflorescence assay, a tumor growth inhibition assay, tumor size reduction assay, a CTL assay, inhibition of tumor metastasis, increase in life expectancy, infectious disease recovery and observation of the health of the mammal" in Claims 80 and 84 represents a departure from the specification and the claims as originally filed. Said passage has no support in the specification and the claims as originally filed.

The "acellular composition" in claims 87-91 has no support in the specification and the claims as original filed.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 74, 81-82, and 87-91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "component of a microorganism cell" in claim 74 is indefinite and ambiguous because it is not clear if the "component" is referring to the DNA, the protein, or the cell wall of which microorganism or cell. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

The "adjuvant" in claim 81 is ambiguous and indefinite because the specification specifically discloses that the claimed method does not require adjuvant (page 14, lines 21-28).

The "area of high lymphatic drainage" in claims 82 and 87 ambiguous and indefinite because the specification does not define said area. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 72, 74, 79-80, 82-84, 87, 89, 90 and 91 are rejected under 35 U.S.C. 102(b) as being anticipated by Issekutz *et al* (Clin Exp Immunol 56(3): 515-23, June 1984; PTO 892).

Issekutz *et al* teach a method of obtaining a sustained CTL response in a mammal such as sheep wherein the reference method comprises delivering an antigen such as live vaccinia virus (acellular) by injecting a single bolus dose of the reference antigen directly into the draining site of the cannulated lymph node (page 516, Materials and methods, in particular). The reference method inherently maintain the antigen in the mammal's lymphatic system over time to induce a CTL response (sustained CTL response) since lymphoblast output 7 days following virus injection and virus specific cytotoxic T cells by chromium release assay were detectable up to two weeks (See abstract, Materials and Methods, in particular). Issekutz *et al* further teach that antigen specific CTL response is detected by antiviral protection assay by challenging the sheep with vaccinia virus (See page 520, abstract, in particular). The reference antigen is sustained in the lymph node otherwise the reference CTL response would not have last over two weeks. Issekutz *et al* teach that antigen specific CTL are found in the efferent lymph form a single immunized lymph node (See abstract, in particular). The selected antigen in the reference is capable of inducing CTL response (See entire document). The selected antigen such as vaccinia is the causative agent of (disease matched) for sheep. Thus, the reference teachings anticipate the claimed invention.

11. Claims 79-80, 83, 86, 87, and 90 are rejected under 35 U.S.C. 102(b) as being anticipated by Grohmann *et al* (J Immunol Methods 137(1): 9-15, March 1991; PTO 892).

Grohmann *et al* teach a method of obtaining a sustained CTL response in a mammal such as mice comprising injecting minute amounts of cell-free antigen such as lysate of highly immunogenic murine lymphoma cells bound to nitrocellulose directly into the lymphatic vessel such as the spleen. The direct injection as taught by Grohmann et al inherently sustained CTL response since the antigen is not being degraded or

susceptible to metabolic clearance. Grohmann et al further teach that selected antigen in the reference is capable of inducing CTL response (See entire document). The reference method of injecting antigen directly into the spleen, which is part of the lymphatic system as disclosed on page 73, line 20. The reference method induces cell-mediated immunity (CTL response) such as delayed type hypersensitivity (DTH) response in vivo upon footpad challenge and/or lyses of tumor target cell (chromium release assay) in vitro (See abstract, Materials and methods, in particular). The reference method of delivering the reference antigen is repeated three times at 15-day intervals (See abstract, Materials and Methods, in particular). Grohmann *et al* teach that intrasplenic immunization is useful not only for stimulating the production of antibody but also for the induction of cell-mediated immunity (CTL response) to antigens that can only be obtained in nanograms amount (See page 14, column 2, last paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 72, 73 and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Issekutz *et al* (Clin Exp Immunol 56(3): 515-23, June 1984; PTO 892) in view of Klavinskis *et al* (J Immunol 157(6): 2521-7, Sept 1996; PTO 892).

The teachings of Issekutz *et al* have been discussed supra.

The claimed invention as recited in claim 73 differs from the teaching of the reference only that the method wherein the antigen is provided in the form of polypeptide.

The claimed invention as recited in claim 78 differs from the teaching of the reference only that the method wherein the antigen is disease matched.

Klavinskis *et al* teach a method of obtaining a sustained inducing CTL response in a mammal such as Rhesus macaques by injecting subcutaneously in the proximity of the iliac lymph node of the macaques a liquid comprising a cell-free antigen such as particulate SIVp27 or SIVgag protein (See title, Material and methods, in particular). The reference antigens are matched with the disease such as Simian HIV (See Materials and methods, page 2522-2523, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the viral antigen as taught by Issekutz *et al* for the protein antigen in the form of a polypeptide or antigen in the form of disease matched as taught by Klavinskis *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Issekutz *et al* teach that antigen specific CTL are found in the efferent lymph form a single immunized lymph node (See abstract, in particular). The claimed antigen in the form of polypeptide is an obvious variation of the teachings of Klavinskis *et al* who teach the use peptide antigen that matched the specific disease for the antigen specific CTL response.

15. Claims 72, 75-76, 87 and 88 rejected under 35 U.S.C. 103(a) as being unpatentable over Issekutz *et al* (Clin Exp Immunol 56(3): 515-23, June 1984; PTO 892) in view of US Pat No. 6,204,250 B1 (of record, March 2001, PTO 892), Coupey *et al* (Cytokine 5(6): 564-9, Nov 1993; PTO 892) and Zinkernagel *et al* (Immunol Rev 156: 199-209, April 1997; PTO 892).

The teachings of Issekutz *et al* have been discussed supra.

The claimed invention as recited in claims 75 and 88 differs from the teaching of the reference only that the method wherein the antigen is provided in the form of a nucleic encoding the antigen.

The claimed invention as recited in claim 76 differs from the teaching of the reference only that the method wherein the antigen is provided in the form of a nucleic acid wherein the nucleic acid encoding the antigen comprises a plasmid, a vector or a recombinant viral vector.

The '250 patent teaches a method of immunizing a mammal such as infant against any target antigen wherein the antigen is delivered in the form of nucleic acid or vector in the host cell that encodes said antigen such as virus or bacteria (See Abstract, column 4, column 7, lines 49-53, claim 14 of '250 patent, in particular). The reference antigen is injected into the infant mammals by any means and route known in the art (See column 8, lines 31-37, in particular). The reference method of inducing cytotoxic T lymphocytes is obtainable independent of immunopotentiatior since the reference method injected only the reference antigen such as plasmid encoding NPV1 in physiological saline in the absence of immunopotentiator such as adjuvant (See column 9, lines 51, in particular).

Coupey *et al* teach injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular).

Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the viral antigen as taught by Issekutz *et al* for the antigen encoding by nucleic acid as taught by the '250 patent for a method of obtaining sustained CTL response in a mammal as taught by Issekutz *et al,* Coupey *et al* and Zinkernagel *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '250 patent teaches that the reference method of inducing cytotoxic T lymphocytes is obtainable independent of immunopotentiatior since the reference method injected only the reference antigen such as plasmid encoding NPV1 in physiological saline the absence of immunopotentiator such as adjuvant (See column 9, lines 51, in particular). Issekutz *et al* teach that antigen specific CTL are found in the efferent lymph form a single immunized lymph node (See abstract, in particular). Coupey *et al* teach that direct injection of antigen to the popliteal lymph node (axillary lymph node) enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular).

16. Claims 72 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Issekutz *et al* (Clin Exp Immunol 56(3): 515-23, June 1984; PTO 892) in view of US Pat No 5,830,452 A (Nov 1998; PTO 892) and US Pat No 5,279,608 (Jan 1994; PTO 892).

The teachings of Issekutz *et al* have been discussed supra.

The claimed invention as recited in claim 77 differs from the teaching of the reference only that the method wherein the antigen is maintained by sustained, delivery of the antigen.

The '452 patent teach a method of obtaining a sustained CTL response such as enhance anti-tumor efficacy by administering cytokine such as IL-2. The '452 patent teach sustained delivery of any compound of interest using a device external to the

mammal such as a computer driven pump (See column 5, lines 57-65, in particular). The reference external device is useful for enhancing the therapeutic index of any compound that is useful to stimulate CTL response such as treating tumors, improving patient compliance and minimizing toxicity (See abstract, in particular).

The '608 patent teaches osmotic pump is suitable for the delivery of any agent such as natural synthetic recombinant peptide, protein, drugs analgesics or combination of agents (See column 6, line 32-35, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made continuously deliver any antigen or drug of interest using a computer driven pump as taught by the '452 patent or osmotic pump as taught by the '608 patent for a method of inducing a sustained CTL response wherein the antigen is maintained by sustained, delivery of the antigen as taught by Issekutz *et al,* the '452 patent and the '608 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because he '452 patent teaches the therapeutic index is enhanced due to patient compliance and minimize toxicity (See column 5, lines 57-65, in particular). The '608 patent teaches osmotic pump is suitable for the delivery of any agent such as natural synthetic recombinant peptide, protein, drugs analgesics or combination of agents (See column 6, line 32-35, in particular).

17. Claims 78 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Issekutz *et al* (Clin Exp Immunol 56(3): 515-23, June 1984; PTO 892) in view of US Pat No 5,830,452 (Nov 1998, PTO 892).

The teachings of Issekutz *et al* have been discussed supra.

The claimed invention as recited in claim 81 differs from the teachings of the reference only that the method further comprises delivering a cytokine.

The '452 patent teach a method of enhancing CTL response such as enhance anti-tumor efficacy by administering cytokine such as IL-2. The reference cytokine is administered in a bolus dose, in a continuous, repeated or sustained manner from a device external to the mammal such as a computer driven pump (See column 5, lines 57-65, in particular). The reference method of using external device is useful for enhancing the

therapeutic index of any compound such as cytokine that is useful to stimulate CTL response such as treating tumors, to improve patient compliance and to minimize toxicity (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to deliver cytokine such as IL-2 that enhances CTL response as taught by the '452 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '452 patent teaches cytokine enhances CTL response (See column 5, lines 57-65, in particular).

18. Claims 83 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Issekutz *et al* (Clin Exp Immunol 56(3): 515-23, June 1984; PTO 892) in view of US Pat No 6,037,135

The teachings of Issekutz *et al* have been discussed supra.

The claimed invention as recited in claim 85 differs from the teachings of the reference only that the method wherein the antigen is a patient-matched antigen.

The '135 patent teaches a method of making patient matched antigen such as MHC class I peptide that matches with patient's allele and binds to the TCR for generating the antigen specific cytotoxic T lymphocyte response (See entire document, column 9, line 5-22, in particular). The reference antigen is useful for inducing antigen specific T lymphocytes response in vaccine against tumor and chronic infection (See entire document, column 16, line 62-65, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '135 patent teaches that patient matched antigen is useful for inducing antigen specific T lymphocytes response in vaccine against tumor and chronic infection (See entire document, column 16, line 62-65, in particular).

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844 or (571) 272-0846 after January 20, 2004. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973 or (571) 272-0841 after January 7, 2004. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist (customer service) whose telephone number is (703) 872-9305.

21. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401. The IFW official Fax number is (703) 872-9306. For After Final, the Fax number is (703) 872-9307.

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